

REMARKS

Applicants gratefully acknowledge withdrawal of the obviousness rejection of Claims 19-22 and 28 based on U.S. Patent 5,589,493 ("Eicken et al") in view of the previously cited article by Thornber, *Chem. Soc. Rev.*, 8, 563-580 (1979). Applicants also acknowledge the new obviousness rejection discussed below.

Applicants have amended Claim 19 (as well as withdrawn Claim 33) to limit the amide substituent R⁵ to hydrogen, alkyl, or a limited number and type of acyl groups and (for Claim 19) to limit substituent Z to Z³. Applicants have amended Claim 20 to remove redundant definitions of G¹, G², and G³ (which are unchanged from Claim 19). Applicants acknowledge the withdrawn status of Claim 33 but again request its rejoinder (as amended herein to expedite its consideration) upon finding their claims allowable.

Sufficiency of Test Data

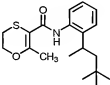
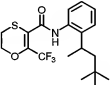
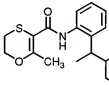
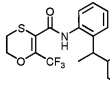
Before addressing the current obviousness rejections and the provisional obviousness-type double patenting rejection, Applicants address challenges to the sufficiency of the data presented in various Declarations under 37 C.F.R. 1.132, including for the first time a third Declaration of Dr. Ulrike Wachendorff-Neumann and a first declaration of Dr. Peter Dahmen, again based on an absence of indications of uncertainty and a supposed inconsistency with unexpectedness. See Final office Action at pages 2-3. Based on context, it also appears that the Final Office Action continues to discount the earlier Declarations of Drs. Wachendorff-Neumann and Voerste. Applicants respectfully submit that the data are not deficient.

It should be apparent that few if any corporate entities would knowingly expend financial resources developing an invention without having a meaningful reason to do so. Because Applicants – and others in the relevant arts – typically screen new compounds using a limited number of test subjects, a strict statistical analysis is generally not conducted due to the small number of samples. However, standard screening tests such as those described in the Declarations at issue (as well as in the specification) have a sufficiently strong track record that those skilled in the art would have confidence in their usefulness as indicators of relative biological activities.

For the convenience of the Examiner, Applicants again summarize their test results in the following tables, which show structures of the tested compounds, the

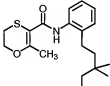
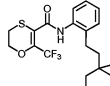
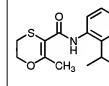
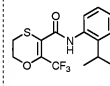
organisms and application rates, and observed test results. Tables 1 and 2 compare inventive trifluoromethyl compounds with comparison methyl compounds, whereas Table 3 compares the effect of alkyl chain length.

Table 1: Summary of Third Declaration of Dr. Wachendorff-Neumann

Test	Efficacy (%)			
	 Comparison Cmpd A ⁽¹⁾	 Inventive Cmpd 2	 Comparison Cmpd B ⁽¹⁾	 Inventive Cmpd 94
<i>Sphaerotheca</i> (cucumber) 100 ppm	78	100	57	93

⁽¹⁾ Comparison compounds from U.S. Patent 5,589,493 ("Eicken et al"); labels A and B are arbitrary identifying labels

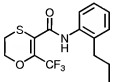
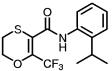
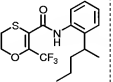
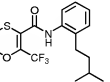
Table 2: Summary of Declaration of Dr. Dahmen

Test	Efficacy (%)			
	 Comparison Cmpd C ⁽¹⁾	 Inventive Cmpd ⁽²⁾	 Comparison Cmpd D ⁽¹⁾	 Inventive Cmpd 39
<i>Puccinia</i> (wheat) 1000 ppm	33	89	—	—
<i>Pyrenophora</i> <i>teres</i> (barley) 1000 ppm	—	—	12	100

⁽¹⁾ Comparison compounds from U.S. Patent 5,589,493 ("Eicken et al"); labels C and D are arbitrary identifying labels

⁽²⁾ Inventive compound not specifically exemplified in the specification but within scope of Applicants' claims

Table 3: Summary of Earlier Declarations

Test	Efficacy (%)			
	 Comparison Cmpd ⁽¹⁾	 Comparison Cmpd 53 ⁽²⁾	 Inventive Cmpd 39	 Inventive Cmpd 102
<i>Alternaria</i> (tomato) 500 ppm (Voerste) ⁽³⁾	0	0	95	—
<i>Sphaerotheca</i> (cucumber) 500 ppm (Voerste) ⁽³⁾	0	0	94	—
<i>Sphaerotheca</i> (cucumber) 100 ppm (W-N D1) ⁽⁴⁾	—	10	—	98
<i>Venturia</i> (apple) 100 ppm (W-N D1) ⁽⁴⁾	—	57	—	100
<i>Uromyces</i> (bean) 100 ppm (W-N D2) ⁽⁵⁾	—	10	95	—

⁽¹⁾ Comparison compound similar to but not identical to cited Hahn et al paper

⁽²⁾ Comparison compound 53 of cited Hahn et al paper

⁽³⁾ Voerste – From Voerste Declaration

⁽⁴⁾ W-N D1 – From first Wachendorff-Neumann Declaration

⁽⁵⁾ W-N D2 – From second Wachendorff-Neumann Declaration

The large differences in the test results fully support Applicants' reasonable belief that the inventive compounds tested were consistently more effective than the comparison compounds, regardless of the presence or absence of a strict statistical analysis. Moreover, Applicants submit that the large – and generally very large – observed differences in test results between the inventive compounds and the comparison compounds are indicative of unexpectedly enhanced efficacy.

Applicants again submit that the Final Office Action at pages 4-5 incorrectly concludes that the data for comparison compound 53 of the Hahn et al paper are unreliable because the *Sphaerotheca* tests reported in two of the Declarations produced different results, thereby "suggest[ing] a statistical problem in the measurements." Applicants again point out that the experiments were not carried out on the same days or in the same laboratories or even under identical conditions. In particular, one set of *Sphaerotheca* tests was carried out under the direction of Dr. Wachendorff-Neumann using a mixture of equal parts acetone and dimethylacetamide as solvent, whereas the other set of *Sphaerotheca* tests was separately carried out under the direction of Dr. Voerste using only dimethylacetamide as solvent. However, even if for the sake of discussion one ignores such differences and assumes that the *Sphaerotheca* tests can be somewhat variable, the large relative differences in efficacies in direct comparisons between comparison compound 53 and inventive compound 39 (as in Dr. Voerste's Declaration) and between comparison compound 53 and inventive compound 102 (as in Dr. Wachendorff-Neumann's first Declaration) are so great that those skilled in the art would reasonably conclude that the inventive compounds exhibit unexpectedly and surprisingly enhanced efficacies compared to the comparison compound. In this respect Applicants again refer to the established principal that "when an applicant demonstrates substantially improved results . . . and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." *In re Soni*, 54 F.3d 746, 751, 34 U.S.P.Q.2d 1684, 1688 (Fed. Cir. 1995) (emphasis added). The absence of any contrary objective evidence, coupled with the large differences in observed efficacies and with the consistently high efficacies found in the other comparison experiments, support Applicants' belief that those skilled in the art would conclude that the compounds of their invention are patentably distinct from the compounds taught by the reference, even in the absence of strict statistical analysis.

Moreover, Applicants maintain that the Final Office Action continues to be overly zealous in discounting the *Sphaerotheca* test data while at the same time improperly ignoring the very strong data from the other tests, including data from other tests that directly compare Applicants' elected species (in particular, the compound of their Example 39) with comparison compound 53 of the cited Hahn et al paper. The data in

the Declarations summarized in Table 3 represent the results from four different tests carried out against four different organisms using two different application rates. In every single test, Applicants' inventive compounds always exhibited very high efficacy, whereas the comparison compounds did not. Even in the *Venturia* test, which gave the "closest" results, the differences in efficacy are dramatic. That is, as Applicants have repeatedly pointed out, Applicants' inventive compounds always exhibited dramatically greater efficacies than the respective comparison compounds, regardless of the organism or application rate, despite only modest structural differences for each tested pair of compounds. In view of these consistently greater efficacies, Applicants maintain that even without a strict statistical analysis, those skilled in the art would conclude that the compounds of their claimed invention are patentably distinct from the compounds taught by the Hahn et al paper. Applicants maintain that the Final Office Action provides no objectively based reason to doubt their showings of enhanced activities.

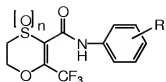
For the reasons discussed below, Applicants maintain that their strong data overcome any inference of obviousness.

Rejections under 35 U.S.C. 103

A. Hahn et al article

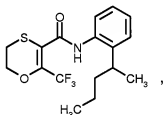
Claims 19-22 and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the cited Korean language paper by Hahn et al. Applicants again point out that the English translation of the Hahn et al paper kindly provided by the Examiner refers to antibacterial activity, whereas the English abstract attached to the original paper refers to antifungal activity. Based on a review of context, Applicants again use the terms "fungicide" or "fungicidal" when referring to or citing the Hahn et al paper. Applicants respectfully traverse.

Applicants maintain that structural features, as well as the biological differences discussed above, are sufficient to distinguish their claimed compounds from the compounds disclosed in the Hahn et al paper. As has been fully discussed in Applicants' previous Amendments, the Hahn et al paper discloses a very limited number and variety of specific dihydro-1,4-oxathiin carboxanilides having the formula



in which n is 0, 1, or 2 and R is hydrogen or one or two of a set of narrowly defined substituents that include methyl, trifluoromethyl, ethyl, isopropyl, methoxy, isopropoxy, methylthio, fluoro, chloro, bromo, nitro, and cyano. Group R of the reference is thus clearly limited to relatively simple groups. Test data for some of these compounds are found in Table 2 of the reference.

Applicants again point out that substituent Z of their claimed compounds must always be attached through a carbon-to-carbon bond to the ortho position of the benzene ring. Applicants' elected species, the compound of Example 39 having the formula



exemplifies these requirements. Although the Hahn et al paper does disclose a few ortho-substituted substituents, only eight of the disclosed compounds have an alkyl group attached at an ortho position (see Table 1 of translation at pages 14 and 15 as previously described in detail), not one of which compounds has an alkyl group having five or more carbon atoms that would correspond to Applicants' unsubstituted C₅-C₂₀-alkyl members of group Z³ or a chlorine- or cycloalkyl-substituted alkyl group that would correspond to Applicants' substituted C₁-C₂₀-alkyl members of group Z³. Nothing in the reference suggests compounds other than those specifically disclosed.

Furthermore, based on test results for specific compounds having substituents R at the meta position, the authors of the Hahn et al paper concluded that "the isopropoxy group or isopropyl group at the meta location of its phenyl group plays an important role" in fungicidal activity of such compounds. See translation at pages 15-16 (emphasis added). In view of the clearly stated preference for substitution of the benzene ring at the meta position with a three-carbon isopropoxy or isopropyl group, Applicants submit

that the Hahn et al paper would not lead those skilled in the art to expect enhanced activity for compounds having longer chain alkyl groups located at an ortho position as required by Applicants.

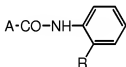
Notwithstanding such differences, the Final Office Action at page 4 again asserts that Applicants' elected species (and by extension their other claimed compounds) is merely a homolog of the known compound 53 and would thus be expected to exhibit similar activity. Even if their claimed compounds might be expected to exhibit some degree of fungicidal activity, Applicants submit that those skilled in the art would expect any such activity to be comparable to that of known compounds, not enhanced activity as found for the tested inventive compounds.

Applicants therefore again respectfully submit that their claimed invention is not rendered obvious by the Hahn et al paper.

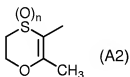
B. Eicken et al in view of Hahn et al article and Silverman article

Claims 19-22, and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,589,493 ("Eicken et al") in view of the cited papers by Hahn et al (discussed above) and by Silverman. Applicants respectfully traverse.

As previously discussed, Eicken et al discloses nicotinic anilide derivative of the formula



in which **R** is any of a host of substituents, including optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkyloxy, phenyl, or halogen, and **A** is optionally substituted pyridin-3-yl or phenyl of any of a number of heteroaromatic groups, one of which can have the formula (A2)



(where n is 0, 1, or 2), used to combat Botrytis. E.g., column 1, lines 8-49, taken with column 17, line 15.

As pointed out in Applicants' previous Amendment, Eicken et al teaches that heteroaromatic group (A2) must always be substituted with a methyl group, not with a trifluoromethyl, difluoromethyl, or cyclopropyl group as specified by Applicants. In this respect, Applicants again refer to the third Declaration of Dr. Wachendorff-Neumann and the Declaration of Dr. Dahmen, which together show the superiority against three different fungi of three inventive compounds in which the G¹ substituent on the oxathiine ring is trifluoromethyl compared to compounds within the scope of Eicken et al in which the corresponding substituent on the oxathiine group (A2) is necessarily methyl. Even when the alkyl side chains on the phenyl moiety are varied, Applicants' inventive trifluoromethyl-substituted compounds were always much more effective against the fungi than the corresponding comparative methyl-substituted compounds.

The Final Office Action at pages 9-10 relies on the Hahn et al paper as teaching alkyl analogs of Applicants claimed invention (discussed above) and on the Silverman paper as teaching increased pharmacological effects with increasing carbon chain length. Applicants respectfully disagree with the conclusions expressed in the Final Office Action.

For reasons similar to those discussed above, Applicants submit that the Hahn et al paper would not lead those skilled in the art to longer chain alkyl substituents at the ortho position of the phenyl group and thus adds nothing not already taught by Eicken et al.

The Silverman paper teaches that the length of carbon side chains can affect the therapeutic index of certain pharmacologically active compounds, presumably due to the effect of chain length on lipophilicity. The Final Office Action, however, fails to establish how this observation relates to compounds akin to those of the present invention or to agricultural applications. Moreover, the Final Office Action fails to take into account the further teaching that "*chain branching* lowers the potency of a compound." See page 18 (emphasis in original). Although Applicants' experiments were not designed to study effects of branching, it may be noted that the data in Table 3 above do not show reduced efficacy that could be attributed to degree or location of branching (and might even show the opposite from what the reference teaches).

Applicants therefore submit that those skilled in the art would conclude that the compounds of their claimed invention are patentably distinct from the compounds taught by Eicken et al, whether taken alone or with the cited Hahn et al and/or Silverman papers.

Double Patenting Rejection

Claims 19-22 and 28 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-3 of copending Application No. 10/588,491. Applicants again note that this application has published as Publication US 2008/0058389. Applicants respectfully traverse. Applicants, although they make no concession about obviousness, again note their offer of an appropriate terminal disclaimer if their claims are otherwise found allowable.

In view of the preceding amendments and remarks, allowance of the claims is respectfully requested.

Respectfully submitted,

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